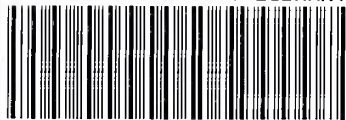


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The Diagnostic Accuracy of Kernig's Sign, Brudzinski's Sign,
and Nuchal Rigidity in Adults with Suspected Meningitis

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**The Diagnostic Accuracy of Kernig's Sign, Brudzinski's Sign,
and Nuchal Rigidity in Adults with Suspected Meningitis**

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Karen Elizabeth Thomas

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THE DIAGNOSTIC ACCURACY OF KERNIG'S SIGN, BRUDZINSKI'S SIGN, AND NUCHAL RIGIDITY IN ADULTS WITH SUSPECTED MENINGITIS. Karen E. Thomas, Rodrigo Hasbun, James Jekel, and Vincent J. Quagliarello. Department of Internal Medicine and Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT.

To determine the diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity, 297 adults with suspected meningitis were prospectively evaluated for the presence of these meningeal signs before lumbar puncture. Kernig's sign (sensitivity = 5%, likelihood ratio positive = 0.97), Brudzinski's sign (sensitivity = 5%, likelihood ratio positive = 0.97), and nuchal rigidity (sensitivity = 30%, likelihood ratio positive = 0.94) did not accurately discriminate patients with and without meningitis (≥ 6 white blood cells (WBC)/ml of cerebrospinal fluid (CSF)). The diagnostic accuracy of these signs did not significantly improve in the subset of patients with moderate meningeal inflammation (≥ 100 WBC/ml of CSF) or in the subset of patients with microbiologic evidence of CSF infection. Only in four patients with severe meningeal inflammation (≥ 1000 WBC/ml of CSF) did nuchal rigidity show diagnostic value (sensitivity = 100%, negative predictive value = 100%). In adults with suspected meningitis, neither the presence nor absence of these classic meningeal signs reliably indicate the presence or absence of meningitis; better bedside diagnostic signs are needed.

Acknowledgements

I gratefully acknowledge the guidance and support of my thesis advisor and mentor, Dr. Vincent J. Quagliarello. I would like to acknowledge the contributions of Dr. James Jekel, who provided statistical expertise, and Dr. Rodrigo Hasbun. Dr. Hasbun received financial support from a National Research Service Award (F32NS09889) and the Bayer Corporation. Finally, I would like to thank Dr. Ralph I. Horwitz, the Department of Internal Medicine, and the Office of Student Research at Yale University School of Medicine for the financial support that allowed me to present this data in poster format at the Infectious Diseases Society of America 39th Annual Meeting.

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Introduction

Adults with suspected meningitis require rapid and accurate clinical evaluation to determine the risk of meningitis and the need for lumbar puncture. Community-acquired bacterial meningitis carries a mortality of approximately 25% despite effective antibiotic therapy, and delays in antibiotic initiation can adversely affect clinical outcome [1-3].

Optimal evaluation of the risk of meningitis requires diagnostic assessment of a patient's clinical features. A recent meta-analysis reported that in adults with suspected meningitis physical signs were more reliable than clinical history in establishing a diagnosis [4]. In this study, individual signs in the clinical history had a low accuracy in diagnosing meningitis. The pooled sensitivity of headache was 50%, and nausea and vomiting, 30% [4]. In contrast, clinical symptoms had diagnostic accuracy values that were clinically useful. Meta-analysis demonstrated that virtually all patients (99-100%) had at least one of the following symptoms: fever, neck stiffness, or altered mental status [4].

Kernig's sign, Brudzinski's sign, and nuchal rigidity are three bedside diagnostic tests used specifically to assess a patient's risk for meningitis. Vladimir Kernig first described the sign that bears his name in 1882, "In the majority of cases of meningitis . . . if one tries to extend the knee while the patient remains sitting, one succeeds only to an angle of about 135 degrees" [5]. Kernig noted that while these contractures may be entirely absent when the patient is lying down, they are often pronounced when the patient is seated. Today, Kernig's sign is considered present when there is extensor spasm of the knee at 135 degrees during passive extension.

Jozef Brudzinski described several physical signs indicative of meningitis; the best known is the nape of the neck sign. In 1909 Brudzinski wrote, “when I made a passive flexion of the neck to convince myself of the stiffness of the latter, I noticed the flexion of the lower limbs in the two joints and the flexion of the lower limbs over the pelvis” [6]. Today, this sign, often simply referred to as Brudzinski’s sign, is considered present when there is flexion of the knees or hip upon passive flexion of the neck.

Nuchal rigidity was known to be a physical finding indicative of meningeal inflammation more than 120 years ago. Both Kernig and Brudzinski were aware of its relation to meningitis. Today, nuchal rigidity is considered present when there is involuntary resistance to passive flexion of the neck.

There are two similarities among the meningeal signs that are worth noting. First, meningeal signs are reflexes, involuntary reactions elicited by the stretching of inflamed meninges. As reflexes, meningeal signs can be elicited in patients who are unresponsive or comatose [7]. Second, the presence of pain is unrelated to the presence of meningeal signs. Although performing these bedside diagnostic maneuvers may elicit pain, the presence of pain does not constitute a positive meningeal sign.

The first investigation of the diagnostic accuracy of Kernig’s and Brudzinski’s signs was conducted by Brudzinski. In 1909, he reported that in patients with bacterial or tuberculous meningitis, Kernig’s sign was 57% sensitive and Brudzinski’s nape of the neck sign was 96% sensitive [8]. Since then, Kernig’s and Brudzinski’s signs have been widely used to assess a patient’s risk for meningitis.

Current data on the diagnostic accuracy of Kernig’s and Brudzinski’s signs are limited to three studies. One study, of 171 episodes of gram negative meningitis,

reported sensitivity values of Kernig's and Brudzinski's signs as 36% and 39% respectively [9]. However, few patients (n=36) were tested for the presence of meningeal signs, and its retrospective data collection is subject to bias since tests for meningeal signs may have been performed after the results of lumbar puncture were known. A second smaller study, which prospectively evaluated 54 patients with fever and recent onset headache, reported sensitivity and specificity values of Kernig's sign as 8.8% and 100% respectively [10]. Brudzinski's sign was not evaluated. A third study, which investigated the presence of meningeal signs in hospitalized elderly patients, reported the specificity of Kernig's sign as 98.5% and the specificity of Brudzinski's sign as 100% [11]. However, meningeal signs were not tested in a cohort of patients in whom these signs are conventionally used, namely patients in whom meningitis is suspected.

Numerous studies have reported diagnostic accuracy values for nuchal rigidity. In patients with meningitis, the calculated sensitivity of nuchal rigidity ranges from 15% to 92% [2,10,12-18]. However, the majority of contemporary studies were based on retrospective data and none were designed with the primary aim of assessing the diagnostic accuracy of nuchal rigidity.

Despite being used as indicators of meningeal inflammation for almost a century, the diagnostic accuracy of these bedside clinical signs has never been rigorously investigated in a prospective manner. The primary purpose of this study was to determine the diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity in a prospective cohort of adults with suspected meningitis.

Methods

Cohort Assembly. Adults (age >16 years) who presented to the Yale-New Haven Hospital Emergency Department between July 1995 and June 1999 with clinically suspected meningitis were eligible for this study. Suspected meningitis was defined as the presence of compatible clinical symptoms (i.e., fever, headache, neck stiffness, photophobia, nausea, and vomiting) such that a lumbar puncture was performed to determine the presence of CSF inflammation. This cohort formed the patient base for a recently published article investigating the utility of head computed tomography before lumbar puncture [19]. Of 301 patients enrolled, 297 underwent lumbar puncture; the remaining four were excluded based on head computed tomography results showing mass effect. This study was approved by the Human Investigation Committee at Yale University School of Medicine; all enrolled patients consented to participate.

Data Collection. All clinical information, including tests for Kernig's sign, Brudzinski's sign, and nuchal rigidity, was gathered and recorded by an emergency-department physician or physician-investigator before lumbar puncture. Enrolling physicians were required to record historical and physical exam findings of research subjects, but they were not given explicit instructions regarding the performance of meningeal signs. All diagnostic and management decisions were at their discretion.

Laboratory Analysis. Laboratory analysis of all cerebrospinal fluid samples included Gram's stain and bacterial culture as well as determination of WBC count, protein, and glucose. Additional CSF analysis (i.e., tests for viral, fungal, or mycobacterial pathogens) were ordered at the discretion of the treating physician. Meningitis was

considered present if cerebrospinal fluid (CSF) white blood cell (WBC) count was ≥ 6 cells per ml.

Statistical Analysis. Bivariate analysis was performed using the chi-square test and the T-test. P values less than or equal to 0.05 were considered statistically significant. Standard definitions of sensitivity, specificity, positive predictive value, and negative predictive value were employed. Likelihood ratio positive (LR+) was calculated by dividing the sensitivity by the false positive error rate. Likelihood ratio negative (LR-) was calculated by dividing the false negative error rate by the specificity. The ratio of LR+/LR- was calculated to represent the overall accuracy of the test. Statistical analysis was performed using SAS software.

Division of Responsibility. The data which form the basis of this study was originally generated for a study investigating the utility of CT scan prior to lumbar puncture [19]. The original study was designed by Dr. Rodrigo Hasbun and Dr. Vincent J. Quagliarello; both investigators agreed their data could be used for this investigation.

Data collection was done by individual clinicians and housestaff in the emergency department at Yale-New Haven Hospital. Attending physicians and post-graduate residents identified eligible patients, obtained consent, collected information on the patient's baseline characteristics, took a clinical history, and performed the physical examination.

I designed the current study investigating the diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity in adults with suspected meningitis. I wrote and submitted the study protocol to the Human Investigation Committee at Yale University School of Medicine. I directed and interpreted analysis of the data with the

help of Dr. James Jekel who performed the data analysis and provided statistical expertise. Finally, I completed a manuscript which has been accepted for publication in *Clinical Infectious Diseases*.

Results

Description of Cohort. Two hundred and ninety-seven adults with suspected meningitis underwent lumbar puncture; cerebrospinal fluid analysis revealed 80 (27%) had objective evidence of meningitis (CSF WBC count ≥ 6 cells per ml). Baseline characteristics and clinical presentation of patients with meningitis were similar to those of patients without meningitis and are shown in Table 1.

Emergency room physicians (28% interns, 55% residents, and 17% attending physicians) gathered the clinical history and conducted the physical examination before performing a lumbar puncture. The most common presenting symptoms overall were headache (84%), fever (68%), nausea and vomiting (58%), photophobia (53%), and neck stiffness (46%). The majority of patients (81%) presented with two or more of these symptoms. The probability of meningitis for different combinations of clinical symptoms characteristic of meningitis ranged from 0.42 to 0.57 (Table 2).

Laboratory Results. Of the 80 patients with CSF evidence of meningitis (≥ 6 WBC/ml of CSF), 29 had evidence of moderate meningeal inflammation (≥ 100 WBC/ml of CSF) and four had evidence of severe meningeal inflammation (≥ 1000 WBC/ml of CSF). Eighteen patients had microbiologic evidence of CSF infection detected either by a positive CSF culture or positive antigen test; the causative pathogens identified included: *Enterovirus* (8), *Cryptococcus neoformans* (6), *Neisseria meningitidis* (2), *Varicella-Zoster Virus* (1), and *Streptococcus pneumoniae* (1). Mean CSF indices, for patients with and without meningitis, are shown in Table 1.

Diagnostic Accuracy of Kernig's and Brudzinski's Signs. Kernig's sign and Brudzinski's sign were tested, prior to lumbar puncture, in a total of 237 and 236 patients

respectively. Seven patients tested positive for Kernig's sign and negative for Brudzinski's sign; seven patients tested positive for Brudzinski's sign and negative for Kernig's sign; four patients tested positive for both meningeal signs. All other patients tested negative for both signs.

Of the 66 patients with meningitis (≥ 6 WBC/ml of CSF), three had a positive Kernig's sign (sensitivity = 5%); of the 171 patients without meningitis, 163 had a negative Kernig's sign (specificity = 95%) (Table 3). Of the eleven patients with a positive Kernig's sign, three had CSF evidence of meningitis (positive predictive value = 27%); of the 226 patients with a negative Kernig's sign, 163 did not have meningitis (negative predictive value = 72%). The sensitivity (5%), specificity (95%), positive predictive value (27%), and negative predictive value (72%) of Brudzinski's sign (Table 3) were identical to those of Kernig's sign. For both Kernig's sign and Brudzinski's sign the likelihood ratio positive (LR+) was 0.97, the likelihood ratio negative (LR-) was 1.0, and the ratio of LR+/LR- was 0.97.

Diagnostic Accuracy of Nuchal Rigidity. Nuchal rigidity was tested in all 297 patients before lumbar puncture. Of the 297 patients tested, 93 had evidence of nuchal rigidity on physical exam. Of the 80 patients with meningitis (≥ 6 WBC/ml of CSF), 24 had nuchal rigidity (sensitivity = 30%); of the 217 patients without meningitis, 148 did not have nuchal rigidity (specificity = 68%) (Table 3). Of the 93 patients with nuchal rigidity, 24 had CSF evidence of meningitis (positive predictive value = 26%); of the 204 patients without nuchal rigidity, 148 did not have meningitis (negative predictive value = 73%). The likelihood ratio positive (LR+) of nuchal rigidity was 0.94, the likelihood ratio negative (LR-) was 1.02, and the ratio of LR+/LR- was 0.92.

The combination of meningeal signs (i.e., testing positive for any one of Kernig's sign, Brudzinski's sign, or nuchal rigidity) had diagnostic values that were virtually identical to those of nuchal rigidity alone (sensitivity = 30%, specificity = 67%, positive predictive value = 25%, negative predictive value = 72%, likelihood ratio positive (LR+) = 0.92, likelihood ratio negative (LR-) = 1.04, and ratio of LR+/LR- = 0.88).

Diagnostic Accuracy of Meningeal Signs in Patients with More Severe Meningitis.

The diagnostic accuracy of Kernig's sign (LR+ = 2.07, LR- = 0.96, ratio of LR+/LR- = 2.15) and Brudzinski's sign (LR+ = 2.06, LR- = 0.95, ratio of LR+/LR- = 2.17) were only marginally improved in the subset of patients (n=29) with moderate meningeal inflammation (≥ 100 WBC/ml of CSF) (Table 4). The same was true for the subset of patients (n=18) with microbiologic evidence of CSF infection (for Kernig's sign: LR+ = 3.3, LR- = 0.90, ratio of LR+/LR- = 3.6; for Brudzinski's sign: LR+ = 1.46, LR- = 0.97, ratio of LR+/LR- = 1.5) (data not shown).

Kernig's sign and Brudzinski's sign did not accurately identify patients with severe meningeal inflammation (≥ 1000 WBC/ml of CSF) (Table 5). However, clinical evidence of meningeal inflammation as manifest by nuchal rigidity did accurately identify all four patients with CSF leukocytosis ≥ 1000 /ml (Table 5). In this small subset of patients, the diagnostic values of nuchal rigidity were as follows: sensitivity = 100%, specificity = 70%, positive predictive value = 4%, negative predictive value = 100%, likelihood ratio positive (LR+) = 3.3, likelihood ratio negative (LR-) = 0. The ratio of LR+/LR- approached infinity.

Discussion

In this prospective study, the three classic meningeal signs—Kernig’s sign, Brudzinski’s sign, and nuchal rigidity—were of limited clinical diagnostic value in adults with suspected meningitis. None of these meningeal signs were able to accurately discriminate patients with meningitis (≥ 6 WBC/ml of CSF) from those without. Furthermore, no significant correlation existed between these meningeal signs and moderate meningeal inflammation (≥ 100 WBC/ml of CSF) or between these meningeal signs and microbiologic evidence of CSF infection. Only in the four patients with severe meningeal inflammation (≥ 1000 WBC/ml of CSF) did nuchal rigidity reveal 100% sensitivity, 100% negative predictive value, and a ratio of LR+/LR- that approached infinity.

In the present study, the sensitivity of both Kernig’s sign and Brudzinski’s sign was 5%, suggesting that in the presence of meningitis, these bedside maneuvers did not reliably identify the need for lumbar puncture. Although the specificity of both signs was 95%, the high specificity values were a result of the overall paucity of positive test results for Kernig’s and Brudzinski’s signs, rather than a reflection of their discriminating ability. The positive and negative predictive values of Kernig’s sign (27% and 72%, respectively), Brudzinski’s sign (27% and 72%, respectively), and nuchal rigidity (26% and 73%, respectively) also indicate that none of the classic meningeal signs were clinically discriminating indicators of the presence or absence of meningitis.

In the setting of meningitis (≥ 6 WBC/ml of CSF), the likelihood ratio positive (LR+) of all three meningeal signs was less than 1; therefore, the post-test probability of meningitis, after performing these diagnostic tests, was less than the pre-test probability.

In addition, the ratio of LR+/LR- of all three meningeal signs was less than 1. Statistical literature suggests that diagnostically useful tests have LR+/LR- ratios of greater than 50 [20]. Therefore, the low values for the ratio of LR+/LR- are additional evidence that these diagnostic tests do not help the clinician identify patients with meningitis. The minimal overlap (n=4) between patients in whom Kernig's sign was positive (n=11) and those in whom Brudzinski's sign was positive (n=11) suggests that examining physicians evaluated each meningeal sign independently and that test results for one meningeal sign did not influence test results of another.

The results of this study demonstrate that the diagnostic accuracy of Kernig's sign and Brudzinski's sign was poor for patients with moderate meningeal inflammation (≥ 100 WBC/ml of CSF), for patients with severe meningeal inflammation (≥ 1000 WBC/ml of CSF), and for patients with microbiologic evidence of CSF infection. The ratio of LR+/LR- did not exceed 10 for either Kernig's or Brudzinski's signs in any of these three subsets. Therefore, our data suggests that even in cases of meningitis which appear more severe on the basis of laboratory evidence, Kernig's and Brudzinski's signs were of little diagnostic value.

Nuchal rigidity was the only meningeal sign that proved to have clinically useful discriminating power. In the four patients with ≥ 1000 WBC/ml of CSF, nuchal rigidity was 100% sensitive and had a negative predictive value equal to 100%. Additionally, in this subset of patients the ratio of LR+/LR- approached infinity. Therefore, in the setting of severe meningeal inflammation, nuchal rigidity was found to have clinically useful discriminating power. This finding is consistent with the general findings of Brudzinski, namely, that meningeal signs can identify cases of severe meningeal inflammation.

In our cohort, only one of the four patients with severe meningeal inflammation had bacterial meningitis. There were two additional patients with proven bacterial meningitis, both of whom had CSF WBC count <1000 . Therefore, while nuchal rigidity accurately identified patients with severe meningeal inflammation, it failed to identify two of the three patients with bacterial meningitis in our cohort.

Two additional findings are worth noting. First, our data is consistent with a recently published meta-analysis [4], that clinical symptoms do not reliably identify patients with meningitis. In our study, the highest probability of meningitis for any combination of clinical symptoms (fever, headache, photophobia, neck stiffness, nausea, and vomiting) was 0.57. Second, our data suggests that bacterial meningitis is uncommon, even among adults in whom meningitis is suspected based on historical features. In our cohort of 297 adults with suspected meningitis, only three (1%) were ultimately diagnosed with bacterial meningitis by a positive CSF culture. This finding, coupled with the potential risks associated with a lumbar puncture [21,22] highlights the need for more reliable clinical means to assess the likelihood of meningitis.

Our study was the first to prospectively determine the diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity in adults with suspected meningitis. Its prospective nature ensured that tests for meningeal inflammation were not influenced by knowledge of laboratory results. Clinically suspected meningitis was chosen as the primary enrollment criterion to include the entire severity spectrum of clinical disease and reduce the possibility of spectrum bias [23,24].

Despite its strengths, our study had limitations. Diagnostic tests in general, and physical examination findings in particular, are subject to individual interpretation and

interobserver variability [25-27]. In our study, descriptions of Kernig's and Brudzinski's signs were not explicitly given to physicians prior to performing the physical examination; thus, the manner in which these meningeal signs were tested was not standardized. However, this was intentional and was designed to reflect actual clinical practice and to enable a determination of the diagnostic accuracy of these meningeal signs as they are currently used in a busy emergency department. Therefore, our observations will be generalizable to other emergency department settings where adults with suspected meningitis are evaluated.

Although our study suggests that the classic meningeal signs did not reliably identify patients with meningitis, it does not identify the reason. Given the design of the current study, several possibilities exist: incorrect performance of the diagnostic signs, poor interrater reliability of the signs, or simply that these meningeal signs are poor diagnostic tools. Future studies which standardize the performance of these diagnostic signs and which evaluate their interrater reliability will further clarify the findings of this initial study.

The sensitivity of Kernig's and Brudzinski's signs was first established nearly 100 years ago in patients with severe bacterial or tuberculous meningitis. Today, evaluation of patients with suspected meningitis is complicated by a number of factors including immunocompromised hosts, a broad spectrum of clinical disease, and a variety of causative pathogens. While the results of this study substantiate the general conclusion of Brudzinski, that bedside meningeal signs can identify patients with severe meningeal inflammation, they also demonstrate that these diagnostic tools are too insensitive to detect the majority of patients with meningitis in contemporary practice. Clinical

decisions regarding further diagnostic testing and the need for a lumbar puncture should not rely solely on the presence or absence of these meningeal signs. Better bedside diagnostic tests are needed.

References

1. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. *N Engl J Med* 1997;336:708-16.
2. Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, et al. Acute bacterial meningitis in adults: a review of 493 episodes. *N Engl J Med* 1993;328:21-8.
3. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. *Ann Intern Med* 1998;129:826-9.
4. Attia J, Hatala R, Cook DJ, Wong JG. Does this adult patient have acute meningitis? *JAMA* 1999;282:175-81.
5. Kernig VM. Ueber ein krankheits symptom der acuten meningitis. *St. Petersburg Medizinische Wochenschrift* 1882;7:398.
6. Brudzinski J. Un signe nouveau sur les membres inferieurs dans les meningites chez les infants (signe de la nuque). *Archives de Medecine Infant* 1909;12:745.
7. Callaham M. Fulminant bacterial meningitis without meningeal signs. *Ann Emerg Med* 1998;18:90-3.
8. Verghese A, Gallenmore G. Kernig's and Brudzinski's signs revisited. *Rev Infect Dis* 1987;9:1187-92.
9. Elmore JG, Horwitz RI, Quagliarello VJ. Acute meningitis with a negative Gram's stain: clinical and management outcomes in 171 episodes. *Amer J Med* 1996;100:78-84.
10. Uchihara T, Tsukagoshi H. Jolt accentuation of headache: the most sensitive sign of CSF pleocytosis. *Headache* 1991;31:161-71.

11. Puxty JAH, Fox FA, Horan MA. The frequency of physical signs usually attributed to meningeal irritation in elderly patients. *J Am Geriatr Soc* 1983;31:590-2.
12. Behrman RE, Meyers BR, Mendelson MH, Sacks HS, Hirschman SZ. Central nervous system infections in the elderly. *Arch Intern Med* 1989;149:1596-9.
13. Domingo P, Mancebo J, Blanch L, Coll P, Net A, et al. Acute bacterial meningitis in the elderly. *Arch Intern Med* 1990;150:1546-7.
14. Gorse GJ, Thrupp LD, Nudleman KL, Wyle FA, Hawkins B, et al. Bacterial meningitis in the elderly. *Arch Intern Med* 1984;144:1603-7.
15. Magnussen CR. Meningitis in adults: ten-year retrospective analysis at a community hospital. *NY State J Med* 1980;80:901-6.
16. Massanari RM. Purulent meningitis in the elderly: when to suspect an unusual pathogen. *Geriatrics* 1977;32:55-9.
17. Rasmussen HH, Sorensen HT, Moller-Petersen J, Mortensen FV, Neilsen B. Bacterial meningitis in elderly patients: clinical picture and course. *Age Ageing* 1992;157:425-30.
18. Sigurdardottir B, Bjornsson OM, Jonsdottir KE, Erlendsdottir H, Gudmundsson S. Acute bacterial meningitis in adults: a 20-year overview. *Arch Intern Med* 1997;157:425-30.
19. Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med* 2001;344:1727-33.
20. Jekel JF, Elmore JG, Katz, DL. *Epidemiology, Biostatistics, and Preventative Medicine*. Philadelphia: W.B. Saunders Company, 1996.

21. Evans RW. Complications of lumbar puncture. *Neurol Clin* 1998;16:83-105.
22. Report on the Quality Standards Subcommittee of the American Academy of Neurology. Practice parameters: lumbar puncture. *Neurology* 1993;43:625-7.
23. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med* 1978;299:926-30.
24. Lachs MS, Nachamkin I, Edelstein PH, Goldman J, Feinstein AR, et al. Spectrum bias in the evaluation of diagnostic tests: lessons from the rapid dipstick test for urinary tract infection. *Ann Intern Med* 1992;117:135-40.
25. Elmore JG, Wells CK, Lee CH, Howard DH, Feinstein AR. Variability in radiologists' interpretations of mammograms. *N Engl J Med* 1994;331:1493-9.
26. Wipf JE, Lipsky BA, Hirschmann JV, Boyko EJ, Takasugi J, et al. Diagnosing pneumonia by physical examination. *Arch Intern Med* 1999;159:1082-7.
27. Lok CE, Morgan CD, Ranganathan N. The accuracy and interobserver agreement in detecting the 'gallop sounds' by cardiac auscultation. *Chest* 1998;114:1283-8.

Tables

Table 1. Baseline Characteristics and Clinical Presentation of 297 Adults with Suspected Meningitis

	Patients ^A		
	Without Meningitis	With Meningitis ^B	Total
	(n = 217)	(n = 80)	(n = 297)
<u>Baseline Characteristics</u>			
<u>Age</u>			
Median years (range)	41 (18-93)	37 (22-92)	40 (18-93)
>60 years, <i>n/total (%)</i>	37/217 (17%)	9/80 (11%)	46/297(15%)
<u>Sex, <i>n/total (%)</i></u>			
Male	97/217 (45%)	37/80 (46%)	134/297 (45%)
Female	120/217 (55%)	43/80 (54%)	163/297 (55%)
<u>Ethnicity, <i>n/total (%)</i></u>			
White	104/217 (48%)	51/80 (64%)	155/297 (52%)
Black	68/217 (31%)	21/80 (26%)	89/297 (30%)
Hispanic	40/217 (18%)	7/80 (9%)	47/297 (16%)
Other	5/217 (2%)	1/80 (1%)	6/297 (2%)
<u>Immunocompetence, <i>n/total (%)</i></u>			
Normal	162/217 (75%)	63/80 (79%)	225/297 (76%)
HIV positive	38/217 (18%)	12/80 (15%)	50/297 (17%)
Immunosuppressive Therapy	17/217 (8%)	5/80 (6%)	22/297 (7%)

Table 1. (continued)

	<u>Without Meningitis</u> (n = 217)	<u>Patients^A</u> <u>With Meningitis^B</u> (n = 80)	<u>Total</u> (n = 297)
<u>Clinical Presentation</u>			
<u>Presenting History, n/total (%)</u>			
Headache ^C	168/207 (81%)	69/75 (92%)	237/282 (84%)
Fever	144/216 (67%)	55/78 (71%)	199/294 (68%)
Nausea and Vomiting ^D	113/213 (53%)	54/77 (70%)	167/290 (58%)
Photophobia	105/206 (51%)	43/75 (57%)	148/281 (53%)
Stiff Neck	97/217 (45%)	38/79 (48%)	135/296 (46%)
Focal Motor Deficit	20/210 (10%)	5/78 (6%)	25/288 (9%)
Focal Sensory Deficit	11/206 (5%)	2/76 (3%)	13/282 (5%)
Seizure	12/214 (6%)	7/79 (9%)	19/293 (6%)
 <u>Presenting Signs, n/total (%)</u>			
Temp >100.4°F	112/217 (52%)	34/80 (43%)	146/297 (49%)
Glasgow Coma Score <13	16/217 (7%)	8/80 (10%)	24/297 (8%)
Nuchal Rigidity	69/217 (32%)	24/80 (30%)	93/297 (31%)
Kernig's Sign	8/171 (5%)	3/66 (5%)	11/237 (5%)
Brudzinski's Sign	8/170 (5%)	3/66 (5%)	11/236 (5%)

Table 1. (continued)

	<u>Patients^A</u>		
	<u>Without Meningitis</u> (n = 217)	<u>With Meningitis^B</u> (n = 80)	<u>Total</u> (n = 297)
<u>Cerebrospinal Fluid Analysis</u>			
Mean (±SD) WBC count/ml	1 (±1)	359 (±1543)	97 (±813)
Mean (±SD) protein (mg/dl) ^E	44 (±37)	90 (±102)	57 (±65)
Mean (±SD) glucose (mg/dl)	69 (±28)	64 (±40)	68 (±32)

Table 1. Footnotes

^APercentages may not add to 100% due to rounding.

^BDefined as ≥ 6 WBC/ml of CSF.

^CStatistically significant difference between those patients with and without meningitis; P value = 0.028.

^DStatistically significant difference between those patients with and without meningitis; P value = 0.009.

^EStatistically significant difference between those patients with and without meningitis; P value = 0.0002.

Table 2. Probability of Meningitis for Different Combinations of Clinical Symptoms

<u>Combination of Symptoms</u>	<u>Pre-test Odds^F of Meningitis</u>	<u>Likelihood Ratio Positive (LR+)^G</u>	<u>Post-test Odds^H of Meningitis</u>
Headache + fever	0.37	1.14	0.42
Headache, nausea + vomiting	0.37	1.32	0.49
Headache, fever, nausea + vomiting	0.37	1.50	0.56
Headache, fever, nausea, vomiting + photophobia	0.37	1.45	0.54
Headache, fever, nausea, vomiting, photophobia + neck stiffness	0.37	1.54	0.57

Table 2. Footnotes

^FPre-test odds were defined as the number of patients with meningitis divided by the number of patients without meningitis. In this cohort the pre-test odds of meningitis were $80/217 = 0.37$.

^GLikelihood ratio positive (LR+) was calculated by dividing the sensitivity by the false positive error rate.

^HPost-test odds were calculated by multiplying the pre-test odds by the likelihood ratio positive.

Table 3. Diagnostic Accuracy of Kernig's Sign, Brudzinski's Sign, and Nuchal Rigidity in 297 Adults with Suspected Meningitis

		<u>Meningitis^I</u>		<u>Total</u>
		<u>Present</u>	<u>Absent</u>	
Kernig's Sign ^J	Present	3	8	11
	Absent	63	163	226
Brudzinski's Sign ^K	Present	3	8	11
	Absent	63	162	225
Nuchal Rigidity ^L	Present	24	69	93
	Absent	56	148	204

Table 3. Footnotes

^IDefined as ≥ 6 WBC/ml of CSF.

^JDiagnostic accuracy values for Kernig's sign: sensitivity = 5%, specificity = 95%, positive predictive value = 27%, negative predictive value = 72%, likelihood ratio positive (LR+) = 0.97, likelihood ratio negative (LR-) = 1.0, ratio of LR+/LR- = 0.97.

^KDiagnostic accuracy values for Brudzinski's sign: sensitivity = 5%, specificity = 95%, positive predictive value = 27%, negative predictive value = 72%, likelihood ratio positive (LR+) = 0.97, likelihood ratio negative (LR-) = 1.0, ratio of LR+/LR- = 0.97.

^LDiagnostic accuracy values for nuchal rigidity: sensitivity = 30%, specificity = 68%, positive predictive value = 26%, negative predictive value = 73%, likelihood ratio positive (LR+) = 0.94, likelihood ratio negative (LR-) = 1.02, ratio of LR+/LR- = 0.92.

Table 4. Diagnostic Accuracy of Kernig's Sign, Brudzinski's Sign, and Nuchal Rigidity in Patients with Moderate Meningeal Inflammation^M

		<u>Moderate Meningeal Inflammation^M</u>		
		<u>Present</u>	<u>Absent</u>	<u>Total</u>
Kernig's Sign ^N	Present	2	9	11
	Absent	21	205	226
Brudzinski's Sign ^O	Present	2	9	11
	Absent	21	204	225
Nuchal Rigidity ^P	Present	15	78	93
	Absent	14	190	204

Table 4. Footnotes

^MDefined as ≥ 100 WBC/ml of CSF.

^NDiagnostic accuracy values for Kernig's sign: sensitivity = 9%, specificity = 96%, positive predictive value = 18%, negative predictive value = 91%, likelihood ratio positive (LR+) = 2.07, likelihood ratio negative (LR-) = 0.96, ratio of LR+/LR- = 2.15.

^ODiagnostic accuracy values for Brudzinski's sign: sensitivity = 9%, specificity = 96%, positive predictive value = 18%, negative predictive value = 91%, likelihood ratio positive (LR+) = 2.06, likelihood ratio negative (LR-) = 0.95, ratio of LR+/LR- = 2.17.

^PDiagnostic accuracy values for nuchal rigidity: sensitivity = 52%, specificity = 71%, positive predictive value = 16%, negative predictive value = 93%, likelihood ratio positive (LR+) = 1.77, likelihood ratio negative (LR-) = 0.68, ratio of LR+/LR- = 2.6.

Table 5. Diagnostic Accuracy of Kernig's Sign, Brudzinski's Sign, and Nuchal Rigidity in Patients with Severe Meningeal Inflammation^Q

		<u>Severe Meningeal Inflammation^Q</u>		
		<u>Present</u>	<u>Absent</u>	<u>Total</u>
Kernig's Sign ^R	Present	0	11	11
	Absent	4	222	226
Brudzinski's Sign ^S	Present	1	10	11
	Absent	3	222	225
Nuchal Rigidity ^T	Present	4	89	93
	Absent	0	204	204

Table 5. Footnotes

^QDefined as ≥ 1000 WBC/ml of CSF.

^RDiagnostic accuracy values for Kernig's sign: sensitivity = 0%, specificity = 95%, positive predictive value = 0%, negative predictive value = 98%, likelihood ratio positive (LR+) = 0, likelihood ratio negative (LR-) = 1.04, ratio of LR+/LR- = 0.

^SDiagnostic accuracy values for Brudzinski's sign: sensitivity = 25%, specificity = 96%, positive predictive value = 9%, negative predictive value = 99%, likelihood ratio positive (LR+) = 5.6, likelihood ratio negative (LR-) = 0.78, ratio of LR+/LR- = 7.2.

^TDiagnostic accuracy values for nuchal rigidity: sensitivity = 100%, specificity = 70%, positive predictive value = 4%, negative predictive value = 100%, likelihood ratio positive (LR+) = 3.3, likelihood ratio negative (LR-) = 0, ratio of LR+/LR- approaches infinity.

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